Impact of initiatinG bioLogics In patients with severe asThma on long-Term OCS or frEquent Rescue steroids (GLITTER): data from the International Severe Asthma Registry

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HIGHLIGHTS BOX

What is already known about this topic?

In real-life, biologic use is associated with significant improvement in asthma outcomes, but their effectiveness has not been established in patients with high oral corticosteroid exposure (HOCS) or compared to continuing with HOCS alone.

What does this article add to our knowledge?

Continued HOCS or switch to biologics were both associated with improvement in severe asthma outcomes. However, HOCS patients who initiated biologics experienced even greater improvements than those who continued with long-term or frequent rescue OCS.

How does this study impact current management guidelines?

These findings may influence guidelines to recommend biologics, even in patients showing improvement on long-term or regular rescue OCS, as a cost-effective strategy to improve outcomes while reducing OCS exposure.

Keywords: biologics; effectiveness; ISAR; oral corticosteroids; real-life

List of Abbreviations:

ADEPT: Anonymized Data Ethics Protocols and Transparency

AR: allergic rhinitis

BEC: blood eosinophil count

BMI: body mass index

Bx: biologic

CRS: chronic rhinosinusitis

EAACI: European Academy of Allergy and Clinical Immunology

ED: emergency department

EMA: European Medicine Agency

EUPAS: European Union Electronic Register of Post-Authorisation Studies

GINA: Global Initiative for Asthma

GLM: generalized linear model

HCRU: healthcare resource utilization

HOCS: high oral corticosteroid exposure

ICS: inhaled corticosteroid

ISAR: International Severe Asthma Registry

IgE: anti-immunoglobulin E

IL: anti-interleukin

LABA: long acting β_2-agonist

NP: nasal polyps

OCS: oral corticosteroids

RCT: randomized controlled trial

SD: standard deviation

SMD: Standardized mean difference

T2: type 2

UAE: United Arab Emirates

UK: United Kingdom

ABSTRACT

BACKGROUND: Effectiveness of biologics has neither been established in patients with high oral corticosteroid exposure (HOCS), nor been compared to effectiveness of continuing with HOCS alone.

OBJECTIVE: To examine the effectiveness of initiating biologics in a large, real-world cohort of adult patients with severe asthma and HOCS.

METHODS: This was a propensity-score-matched, prospective cohort study using data from the International Severe Asthma Registry (http://isaregistries.org/). Between January 2015 and February 2021, patients with severe asthma and HOCS (long-term OCS ≥1 year or ≥4 courses of rescue OCS within a 12-month period) were identified. Biologic initiators were identified and, using propensity scores, matched 1:1 with non-initiators. The impact of biologic initiation on asthma outcomes were assessed using generalized linear models.

RESULTS: We identified 996 matched pairs of patients. Both groups improved over the 12-month follow-up period, but improvement was greater for biologic-initiators. Biologic initiation was associated with a 72.9% reduction in the average number of exacerbations/year versus non-initiators (0.64 vs 2.06, rate ratio: 0.27 [95%CI, 0.10, 0.71]). Biologic initiators were 2.2 times more likely than non-initiators to take a daily long-term OCS dose <5mg (probability: 49.6% vs 22.5%; p=0.002) and had a lower risk of asthma-related emergency department visits (relative risk: 0.35 [95% CI: 0.21, 0.58]; rate ratio 0.26 [0.14, 0.48]) and hospitalizations (relative risk: 0.31 [95% CI: 0.18, 0.52]; rate ratio 0.25 [0.13, 0.48]).

CONCLUSIONS: In a real-world setting, including patients with severe asthma and HOCS from 19 countries, and within an environment of clinical improvement, initiation of biologics was associated with further improvements across multiple asthma outcomes, including exacerbation rate, OCS exposure, and healthcare resource utilization.

Introduction

Severe asthma refers to asthma that is uncontrolled despite high dose inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA), or that requires high dose ICS/LABA to remain controlled.[1] It is thought to affect up to 10% of the total asthma population[2] and is associated with significant morbidity, mortality, and socioeconomic burden.[3,4] Recent global characterization analyses showed the high treatment burden associated with severe asthma(over one-third of patients with severe asthma were on Global Initiative for Asthma (GINA) step 5 treatment, and over half received intermittent oral corticosteroid (OCS) bursts[5]) and the predominance of the eosinophilic phenotype.[6] Despite this high treatment burden, it has been reported that over half of these patients had poorly controlled disease and experienced >1 exacerbation per year on average.[5] As a consequence, healthcare costs in severe asthma are disproportionately high, with direct costs higher than for type 2 diabetes, stroke, or chronic obstructive pulmonary disease,[7] and total costs accounting for more than 60% of total asthma expenditure.[8]

ICSs represent the cornerstone of asthma treatment.[1] However, there are two major limitations associated with their use, namely local and systemic side effects that are more common at higher doses, and the persistence of exacerbations and poor control seen in some patients, predominantly among those with severe disease.[9,10] For example, a survey in the United Kingdom (UK) found that 64% of patients with asthma taking ICS reported ≥1 side effect.[11] GINA recommends short-course OCS for those on medium-dose maintenance ICS/formoterol (Step 4) whose initial presentation is with severely uncontrolled asthma, or with an acute exacerbation.[1] Low-dose maintenance OCS is also one of the options that may be added at Step 5 to high dose ICS/LABA to control symptoms and minimize future exacerbation risk.[1] However, the cumulative burden of OCS, from short-course and maintenance doses is associated with adverse effects including obesity, diabetes, osteoporosis, cataracts, hypertension, and adrenal suppression, as well psychological side effects such as depression and anxiety.[12] Indeed, even short-term OCS use is associated with sleep disturbance and increased risk of infection, fracture, and thromboembolism.[13] Strategies to minimize need for OCS are, therefore, a high priority.[1] According to OCS stewardship statements supported by the American College of Allergy Asthma & Immunol and the American Lung Foundation (among others),[14] '*it is time to protect patients*

with asthma from potential over-exposure to OCS and to recognize OCS overuse for what it often is: a treatment plan failure'.[14]

Biologics (including anti-immunoglobulin [Ig]-E), anti-interleukin [IL]5/5R, anti-IL4Rα, and anti-TSLP), that target key mediators of the type 2 (T2) inflammatory cascade can be effective strategies to achieve that aim. They are recommended for patients with severe asthma with exacerbations or poor symptom control on high dose ICS/LABA, who have increased levels of T2 biomarkers (e.g., high blood eosinophil count) or need maintenance OCS.[1] Their efficacy and safety is well-established within the randomized controlled trial (RCT) setting.[15] A systematic review comparing the five current biologics to standard of care for severe eosinophilic asthma found that there is high certainty that all approved biologics reduce the rate of severe asthma exacerbations and—for benralizumab, dupilumab, and mepolizumab—for reducing OCS.[15] However, these confirmatory efficacy studies are limited by restrictive eligibility criteria, relatively small patient populations, and varying study methodology. As such, the generalizability of individual study results to the broader asthma population is limited.[16]

In real life, biologic use has been associated with a significant improvement in lung function and asthma control, and a reduction in the number of asthma exacerbations and OCS use.[17–20] However, the majority of these real-life studies have been small, have used different definitions of severe asthma and asthma exacerbations, and included patients receiving widely varying OCS doses at baseline. Effectiveness of biologics has neither been established in high OCS exposure (HOCS) patients, nor been compared to effectiveness of continuing with HOCS alone and not initiating biologic therapy.[16]

Our aim was to examine the effectiveness of initiating biologics in a large real-world cohort of adult patients worldwide with severe asthma and HOCS.

Methods

Study design and data source

This was a propensity-score-matched, prospective cohort study using data from the International Severe Asthma Registry (ISAR; https://isaregistries.org/). Registry details have been described elsewhere.[21] We included data from 19 countries (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, South Korea, Saudi Arabia, Spain, Taiwan, United Arab Emirates, and the UK) that shared data with ISAR between January 2015 and February 2021. The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPAS33582) and with all applicable local and international laws and regulation. The ISAR database has ethical approval from the Anonymized Data Ethics Protocols and Transparency Committee (ADEPT0218).

Patients

Patients were required to be aged ≥18 years at enrolment and have severe asthma (i.e., receiving treatment at GINA 2018 Step 5 or with uncontrolled asthma at GINA Step 4).[22] See **Table E**1 for Individual registry diagnostic and severe asthma criteria. Biologic prescription criteria variability between ISAR-participating countries has been published elsewhere.[23] Patients were also required to have a history of HOCS use defined as: long-term use of OCS for at least 1 year or ≥4 courses of rescue steroid bursts during the 12-month baseline period. The latter was agreed *a priori* and in line with previous publications.[24] HOCS patients were divided into the biologic-initiated group (who received biologics (anti-IgE, anti-IL5/5R, and anti-IL4Rα) and the biologic-not-initiated group (who were never administered a biologic). Effectiveness was assessed from the date of biologic initiation in the biologic-initiated group (which for some patients was before the first ISAR visit) and from the date of study entry for the biologic-not-initiated group. Various demographic and clinical variables of interest were retrieved at this date (e.g. age, gender, ethnicity, and smoking status). An intention-to-treat approach was applied, in which patients remained in the groups to which they were originally assigned, regardless of any potential changes of treatment (e.g., stopped HOCS) over time. Previously, we found that only 10% of ISAR patients who initiated biologics stopped treatment.[25] Patients with a history of bronchial

thermoplasty, prior history of biologic use, or with inadequate background data at the date of initiation were excluded.

Propensity score matching

Propensity score matching was required as patients with severe asthma and HOCS who initiated biologics have different clinical characteristics than those who do not. These data have been published in detail elsewhere.[26] It was performed to obtain unbiased effectiveness estimates by comparing patients with severe asthma and HOCS who initiated biologics to those with similar clinical characteristics but who did not. Missing data were imputed using a robust multiple imputation approach before matching. Propensity score was derived using logistic regression, with initiation of biologics as the dependent variable. Covariates included age, gender, ethnicity, age at asthma onset, body mass index (BMI), blood eosinophil count (BEC), smoking status, use of invasive ventilation, positive allergen test, presence of allergic rhinitis, chronic rhinosinusitis, eczema, nasal polyps, atopic condition, and geographical locations; all these covariates were measured at baseline, defined as within the past 12 months of biologic initiation or study entry for the biologic initiated and not initiated groups, respectively. Of note, following expert recommendation, outcome history covariates were excluded in the matching to ensure objectivity of the study design.[27] A 1:1 nearest neighbor matching with replacement and subsequent regression analyses was then performed, such that the non-biologic patients could be matched to one or more biologic users (see online repository text).

Outcome variables

The primary outcome was reduced rate of asthma exacerbations with initiation of a biologic therapy, compared to non-initiation. The secondary outcomes included improvement in asthma control, reduction in OCS dose, reduced number of asthma-related emergency department (ED) visits and asthma-related hospital admissions. The exploratory outcome included reduced risk of OCS-related co-morbidities. All outcomes were estimated during a 365-day follow up period. Definitions and longitudinal measurement are provided in **Table E2**.

Statistical Analyses

The statistical analysis plan was pre-defined and analyses performed using Stata version 17 (College Station, TX, USA). Continuous and categorical data were described as mean (standard deviation) and n (%), respectively. Overall, we performed generalized linear models (GLM; with the choice of the distribution and link function depending on the nature of the dependent variable) with generalized estimating equations to obtain robust inference by accounting for clustering (matched pairs and time-series measurements of specific outcomes). All regression analyses were adjusted for follow-up period (i.e., follow-up days were included either as a covariate in the linear and logistic regressions, or as an off-set variable in the Poisson and negative binomial regressions, for the specific type of outcomes). The impact of biologic initiation on outcomes was estimated as marginal effects during the first 365 days of follow-up. Outcomes were not reported for all patients as our study included 9 longitudinal outcomes with different data types (e.g., censored count and binary data, time-series multinomial data), which were measured at irregularly-repeated real-world clinic visits over time. To prevent uncertainty in assumption and potential bias associated with the use of complex imputation methods, we did not impute missing outcome data. The missing pattern of outcome data and the number of observations included in each outcome is provided in **Table E3**.'Additional details are provided in the online repository text.

Primary analysis

A GLM with negative binomial distribution was used to estimate change in rate of exacerbations due to biologic initiation. Using a special causal inference technique (i.e. G-computation), covariate-adjusted effects of biologic initiation were estimated overall, and according to age category, sex group, smoking status, BMI category, and eosinophilic phenotype (**Figure E1**), with further adjustments for exacerbation history and variables whose distribution was still unbalanced (defined as standardized difference >0.25 after matching),[28] (i.e. smoking status and ethnicity).

Secondary analyses

A GLM with multinomial distribution was used to estimate the change in OCS dose due to biologic initiation. OCS dose was categorized in two ways: (i) total cumulative OCS dose per day during follow-up, which included maintenance and burst dose and (ii) long-term cumulative OCS dose per day, which

included maintenance dose only. Both total and long-term daily cumulative OCS dose reduction from baseline to follow-up were categorized as: increased dose (<0% reduction), low dose reduction (0% to ≤50%), moderate dose reduction (>50% to ≤75%), and optimal dose reduction (>75%). An additional logistic regression was used to assess the likelihood of achieving low OCS use, with an OCS dose of <5 mg used to define both low total dose and low long-term dose. Independent variables were the same as the main OCS model. A GLM with multinomial distribution was used to assess change in asthma control. Healthcare resource utilization (HCRU) was assessed using a 2-part GLM separately for asthma-related ED visits and asthma-related hospitalizations. The first part was a probit model to estimate the probability of having any outcome event during follow-up, the second part involved a negative binomial model to estimate the number of outcome events for those who had at least one event. An exploratory logistic regression was used to assess the incidence of any OCS-related co-morbidities and any OCS-related chronic co-morbidities (median follow-up period 721 days; interquartile range: 366-1182 days). All secondary analysis regressions were adjusted for unbalanced propensity score variables, exacerbation history, and the history of the corresponding secondary outcome.

Results

Patients

Between January 2015 and February 2021, of 10,606 adult patients with severe asthma from 19 ISAR participating countries, there were 5379 prospectively recruited patients, of whom 1412 had HOCS during the baseline period and met the inclusion criteria. The median follow-up period was 597 days, with an interquartile range of 360 to 964 days. Among these patients, 996 (70.5%) initiated biologics and 416 (29.5%) did not (**Figure 1**). All those who initiated a biologic were kept and matched with those who did not initiate a biologic (with replacement) yielding 996 patients per group (**Figure 1**). Of those who initiated a biologic, the majority (n=604, 62.7%) were prescribed mepolizumab, followed by omalizumab (n=260; 27.0%). Relatively small proportions of patients initiated benralizumab (n=82; 8.5%), reslizumab (n=12; 1.2%), and dupilumab (n=6; 0.6%).

Baseline characteristics: propensity matching

Post-propensity score matching, biologic-initiated and not-initiated cohorts were well-balanced for age, gender, ethnicity, age of asthma onset, BMI, BEC, smoking status, history of invasive ventilations, testing positive for allergen tests (either skin prick test to aeroallergens or serum specific IgE to aeroallergens), atopic sensitization (being recorded as atopic), and the incidence of relevant co-morbidities and country (**Table 1A; Figure 2)**.

The pre- and post-matching baseline characteristics are summarized in **Table E4** and the propensity score distribution is displayed in **Figure E2**. Of note, although eosinophilic gradient phenotype was not a propensity scoring variable, most matched patients from both the biologic-initiated and not-initiated groups were in ISAR eosinophilic grade 3: most likely eosinophilic (89% and 75%, respectively) (**Table E4**). Patients were also well matched for asthma exacerbation rate, long-term and total OCS dose, asthma control, and HCRU (**Table 1B**). See **Figure E3** for prevalence of OCS-related co-morbidities per group.

Change from baseline in key efficacy variables

Improvement from baseline in asthma exacerbations, asthma control and reductions in HCRU (i.e. asthma related ED visits and hospitalizations), was noted both in those who initiated and those who did not initiate biologic therapy. However, the improvements were greater in those who started biologics (**Figure 3A-D**). For example, over a 12-month follow-up period, patients who initiated a biologic experienced an 88.0% reduction in exacerbation rate, compared with a 58.8% reduction in the biologic-not-initiated group (**Figure 3A**). A similar differential between biologic-initiated and not-initiated groups was noted for asthma control (**Figure 3B**), with superiority of biologic-initiated (vs not-initiated) also observed for the number of ED visits (**Figure 3C**) and hospital admissions (**Figure 3D**).

Exacerbation rate

In the regression analysis of propensity score matched cohorts, biologic initiation was associated with an estimated average reduction of 1.43 exacerbations per year relative to the biologic-not-initiated group in the first year (0.64 vs 2.06, rate ratio=0.27 [95% CI, 0.10, 0.71]), corresponding to a 72.9% reduction. **(Figure 4)**. This pattern of estimated rate reduction remained consistent across age, gender, smoking status, BMI, and eosinophilic phenotype categories**.**

OCS exposure

Patients who initiated a biologic were 2.48 times more likely to achieve a daily total OCS dose (i.e., maintenance plus burst) <5 mg compared to the biologic-not-initiated group (estimated risk probability of 38.0% vs 15.3%; p=0.011) and 2.20 times more likely to achieve a daily long-term OCS dose (i.e., maintenance dose only) <5 mg (risk probability 49.6% vs 22.5%, p=0.002). Compared to those who did not initiate a biologic, those who initiated a biologic were also 3.82 times (95% CI: 1.58, 9.25) more likely to have a moderate (50 to ≤75%) total OCS reduction from baseline (probability of 16.2% vs 5.5%; p=0.001) and tended to be 7.73 times (95%CI: 0.71, 84.27) more likely to have an optimal (>75%) total OCS reduction (risk probability 13.4% vs 3.3%; p=0.063) (**Table 2**).

Asthma control and OCS-related co-morbidities

No significant difference in the likelihood of having controlled asthma was observed within the first year (biologic-initiated vs not-initiated relative risk for staying uncontrolled was 0.66 [95% CI: 0.37, 1.16]).

Likewise, the 365-day risk of any new OCS-related comorbidity was very low in both groups, and the difference was uncertain given the wide confidence intervals of relative risks (**Table 3**).

Healthcare resource utilization

Initiation of biologics was associated with a reduction in risk of asthma-related ED visits by 0.09, corresponding to a 65.0% reduction (p=0.003) compared to the biologic-not-initiated group. Adjusted ED visits in the first year were 0.12 for those who initiated biologics compared to 0.33 for those who did not (rate ratio=0.26 [95% CI: 0.14, 0.48]) (**Table 4**). Biologic therapy initiation was also associated with a 0.07 reduction in risk of experiencing any asthma-related hospitalizations (69% reduction; p=0.001), with the first-year frequency of asthma-related hospitalizations of among the biologic-initiated group being 25% of that of the biologic-not-initiated group (95% CI: 0.13, 0.48; **Table 4**).

Discussion

Accurate estimation of biologic effectiveness in real life is important, as it may influence guideline recommendations for biologic use, as well as access to, choice, and cost-effectiveness of prescribed biologics. In this global study, we assessed biologic effectiveness across a range of clinical outcomes, in patients with severe asthma and HOCS to reflect the overuse and over-reliance on OCS in real-life,[14,31] considering their potential to cause serious side effects and irreversible harm.[12,13] We found that improvement in exacerbation rate, asthma control, and HCRU occurred in patients with severe asthma and HOCS irrespective of subsequent biologic initiation, highlighting the value of severe asthma services especially in terms of background therapy choice and adherence. However, those patients who initiated biologics showed the greatest improvements, exhibiting a 72.9% greater reduction in exacerbation rate and approximately one-third the risk and frequency of asthma-related ED visits and hospitalizations (i.e. serious exacerbations) compared to patients who did not initiate a biologic treatment. These additional benefits are likely caused by direct effects of biologics themselves over and above those associated with tertiary care management in these patients with evidence of eosinophilic asthma, a phenotype associated with more severe exacerbations and poorer asthma control.[32] Initiation of biologic therapy may also have cost-saving potential considering the mean direct cost of treating a hospitalization for a severe exacerbation has recently been estimated at €4997 per exacerbation.[33] This superiority of biologics was noted within an environment of improving asthma control in both groups as well as reduced OCS exposure in the biologic group. Patients who initiated biologics had a 2-times higher chance of achieving a daily long-term OCS dose <5 mg and a 4-times higher chance of reducing their total OCS dose by >75% from baseline than patients who did not initiate a biologic.

Despite available care, recurrent asthma exacerbations are an issue in a proportion of patients with severe asthma.[2,34] RCT data has found a biologic-associated reduction in exacerbation rate of 49% for benralizumab,[35] 47% for mepolizumab,[36] 26% for omalizumab,[37] 41-50% for reslizumab,[38] and 48% for dupilumab,[39] compared to a 58.8% reduction compared to biologic non-initiators and an 88.0% reduction relative to baseline observed in the current study (all biologics combined). This is remarkably similar to the 81% reduction in exacerbation rate recently reported for benralizumab in a real-life cohort of patients with severe asthma in the UK, an effect that was independent of previous biologic use.[40] Improved effectiveness of biologics in the current study may be a consequence of a broader and more

heterogenous population, the size of the study, or differences in the extent of OCS exposure and associated baseline exacerbation rate in the populations studied. Biologic use has also previously been associated with exacerbation rate reduction outside the controlled settings of RCTs, but results have been variable (ranging from a 30 to 69% reduction),[19,41,42] likely due to differences in the background characteristics of the biologic users in real-world settings. Our findings and those of others, therefore, confirm the usefulness of biologics in reducing the considerable exacerbation burden experienced by patients with severe asthma, and their potential for cost-saving in terms of reduced HCRU. Indeed, in the current study, biologic use was associated with a marked reduction in the risk of asthma-related hospitalizations.

It has been estimated that up to 60% of patients with severe asthma are prescribed OCS,[43] and although OCS undoubtedly have a place in short bursts for the treatment of exacerbations, steroid-related adverse events are common.[13] Several steroid sparing strategies are now available to physicians including referral to specialist asthma centers, improving adherence to treatment, adding on therapies like long-lasting muscarinic antagonist and macrolides, and treating with biologics.[1,43] In our study, patients treated with biologics were 2.48 times more likely to have a moderate long-term OCS reduction and 2.20 times more likely to achieve a daily long-term OCS dose <5 mg, in agreement with other real life studies, albeit in small numbers of patients.[17,19,44] For example, the REALITI-A study found that mepolizumab reduced daily OCS by 50% after 21-24 weeks of treatment.[19] The value of OCS reduction with biologic therapy is clear, but perhaps we can be even more aggressive and institute personalized OCS tapering algorithms, as advocated by the PONENTE trial.[45] Real-world evidence is needed to bridge the gap between clinical trials and clinical practice and to examine the long-term impact of steroid reduction on new OCS-related adverse events.

We found no difference in asthma control between the biologic-initiated and biologic-not-initiated groups; both groups showed marked improvement in asthma control from baseline (see **Figure 2B**). This could be a consequence of referral to, and management in, a severe asthma service. Detection of a positive control signal was also challenging in the current study as control was assessed categorically making it more difficult to show a small change, particularly in an environment of clinical improvement. Interestingly, the European Academy of Allergy and Clinical Immunology (EAACI) also concluded in its recent systematic review of biologics that although some biologics probably improve asthma control

with moderate certainty of evidence, none of them showed an improvement above the minimal important difference threshold of 0.5.[15] Others have postulated that this may be because either asthma control does not indicate improvements caused by reduced eosinophilic airway inflammation, or that a dissociation exists between symptoms and exacerbations in patients with severe asthma.[46] We also did not see the expected reduction in new incidence of OCS-related co-morbidities in the biologic-initiated group, but our study was not designed to do so, and the few observed incidences and wide confidence intervals introduced a high level of uncertainity in these findings. However, the patients in biologic-initiated group were more likely to have an OCS dose reduction than patients in the biologic-not-initiated group. A longer-follow up time may be required to observe this effect. Others have also found a disconnect between OCS reduction and toxicity.[47]

Limitations

Limitations of this study include those common to all observational studies, such as recall bias, as well as the potential for an initiation bias due to differences in socioeconomc and geographical factors not acounted for in the matching. Results may have been influenced by missing data, the uneven distribution of patients on each biologic, which was a consequence of the date of data development and requirement for a 1-year follow-up period, and inter-country variability in biologic access criteria.[23] This latter issue has been mitigated in another ISAR study, which found that anti-IL5/5R biologics were more effective than anti-IgE, in patients eligible for, and with access to, both classes.[48] In addition, there may be some confounding by country (e.g., the UK was over represented in the biologic-initiated group, which may have skewed findings); however, this was accounted for during propensity score matching. Strengths of our study are the inclusion of a large, multi-national severe and heterogenous asthma cohort, generalizable to the severe asthma population. Rigorous statistical analyses were also employed, including use of weighted and adjusted regression models and marginal effect estimates, and the potential for bias minimized by use of propensity score matching and multiple imputation.

Conclusions

In conclusion, in a real-world setting, initiation of biologics is associated with reduced exacerbation rate, OCS exposure, and HCRU in patients with severe asthma and HOCS.

Ethics Approval

This study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPAS33582) and with all applicable local and international laws and regulation. Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). Governance was provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (registration number: ADEPT0420). All data collection sites in the International Severe Asthma Registry (ISAR) have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations

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Data Availability

In line with ISAR governance restrictions, sharing individual deidentified participant data is subject to the consent of the ISAR steering committee (ISC) members in accordance with patient consent, patient confidentiality, and ethical considerations. The study documents (protocol, statistical analysis plan, clinical study report) will be made available in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS38128). Proposals should be directed to info@isaregistries.org; to gain access, if approved by the regulatory boards, data requestors will need to sign a data access agreement.

Author Contributions

David B. Price agrees to be accountable for all content and aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in data acquisition or analysis and interpretation, as well as the critical revision of the manuscript for important intellectual content. Wenjia Chen, Trung N. Tran, David B. Price, and Marianna Alacqua were involved in the conception and design of the study. Wenjia Chen and Nigel Chong Boon Wong performed the data analysis. Ruth Murray was responsible for drafting the manuscript and data interpretation. Nasloon Ali, Con Arti, Lakmini Bulathsinhala and Anthony Newell provided additional administrative, technical, and material support. The study was supervised by David B. Price. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

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947 **Table 1A: Post-matching baseline characteristics of propensity scoring variables**

	Bx initiated (n=996)	Bx not initiated (n=996)	SMD
Age, years			
Mean (SD)	51.7 (13.9)	51.1 (14.6)	-0.04
Gender, n (%)			
Male	387 (38.9)	296 (29.7)	0.19
Female	609 (61.1)	700 (70.3)	
Ethnicity, n (%)			
Caucasian	689 (69.2)	682 (68.5)	
Asian	62 (6.2)	65 (6.5)	
African	36 (3.6)	42 (4.2)	0.34*
Mixed	17 (1.7)	55 (5.5)	
Other	83 (8.3)	108 (10.8)	
Unknown	109 (10.9)	46 (4.6)	
Age of asthma onset, years			
Mean (SD)	28.4 (18.7)	28.2 (18.8)	-0.01
BMI (kg/M^2),			
Mean (SD)	29.3 (6.8)	28.5 (7.4)	-0.11
BEC (n/ml)			
Mean (SD)	479.8 (469.7)	527.4 (471.3)	0.10
Smoking status, n (%)			
Current smoker	25 (2.5)	70 (7.0)	
Ex-smoker	285 (28.6)	210 (21.1)	0.27*
Non-smoker	686 (68.9)	716 (71.9)	
Invasive ventilation, n (%)	69 (6.9)	138 (13.9)	0.23
Positive allergen test, n (%)	618 (62.0)	623 (62.6)	0.04
Allergic rhinitis, n (%)	313 (31.4)	302 (30.3)	0.08
Chronic rhinosinusitis, n (%)	246 (24.7)	167 (16.8)	0.20
Eczema, n (%)	98 (9.8)	61 (6.1)	0.14
Nasal polyps, n (%)	351 (35.2)	266 (26.7)	0.19
Atopic sensibilization, n (%)	819 (82.2)	866 (86.9)	0.13
Country, n (%)			
Argentina	1 (0.1)	1 (0.1)	
Australia	43 (4.3)	43 (4.3)	
Bulgaria	4 (0.4)	3 (0.3)	
Canada	23 (2.3)	26 (2.6)	
Colombia	1 (0.1)	1 (0.1)	0.22
Denmark	170 (17.1)	124 (12.4)	
Greece	10 (1.0)	9 (0.9)	
India	0 (0.0)	0 (0.0)	
Ireland	0 (0.0)	0 (0.0)	
Italy	136 (13.7)	132 (13.3)	
Japan	6 (0.6)	8 (0.8)	
Kuwait	70 (7.0)	73 (7.3)	
Mexico	9 (0.9)	3 (0.3)	
Saudi Arabia	15 (1.5)	18 (1.8)	
South Korea	2 (0.2)	1 (0.1)	
Spain	7 (0.7)	7 (0.7)	
Taiwan	4 (0.4)	3 (0.3)	
UAE	0 (0.0)	0 (0.0)	

UK	495 (49.7)	547 (54.9)	

BEC: blood eosinophil count; BMI: body mass index; Bx: biologic; SD: standard deviation; SMD: standardized mean difference; UAE: United Arab Emirates. *Following guideline recommendation, a standardized difference ranging 0.1 or 0.25 represents acceptable standardized biases. Covariates with a standardized difference >0.25 were adjusted in the regression analyses.

Table 1B: Post-matching baseline clinical characteristics

	Bx initiated (n=996)	**Bx not initiated (n=996)**	**SMD**
No. asthma exacerbations in the past year Mean (SD)	5.1 (4.1)	5.0 (3.8)	-0.02
Long-term OCS, n (%)	612 (61.4)	508 (51.0)	0.21
Total daily OCS Dose, mg Mean (SD) Interquartile range	16.11 (15.69) 6.64-16.58	12.45 (7.31) 8.29-21.10	-0.299
Long-term daily OCS Dose, mg Mean (SD) Interquartile range	12.72 (8.92) 5.00-12.50	9.99 (6.21) 5.00-20.00	-0.356
Asthma Control, n (%)* Well controlled Partially controlled Not controlled	51 (6.0) 98 (11.6) 628 (74.2)	35 (4.1) 98 (11.6) 713 (84.3)	0.12
Emergency department visits Mean (SD)	1.7 (4.3)	1.8 (3.7)	0.02
Hospital admissions Mean (SD)	0.9 (2.0)	0.9 (1.6)	0.00
ICS Adherence, n (%) Adherent Poor: Clinical impression Poor: Prescription records	774 (88.7) 12 (1.4) 87 (10.0)	603.5 (69.7) 74.8 (8.6) 187.5 (21.7)	0.50

ICS: inhaled corticosteroids; OCS: oral corticosteroid; SD: standard deviation; SMD: standardized mean difference. Assessed by GINA control critiera[1], Asthma Control Questionnaire,[29] or Asthma Control Test,[30]

Table 2: Effectiveness of biologic initiation versus non-initiation on OCS reduction in 365 days.

	Bx not initiated	Bx initiated	Marginal difference in % probability (95% CI)	Relative risk (95% CI)
Total OCS				
% With:	N=331*	N=1071*		
Increased dose	27.6	16.0	-11.6 (-29.8, 6.7)	0.51 (0.17, 1.51)
Low reduction	63.6	54.4	-9.2 (-24.8, 6.4)	0.87 (0.61, 1.24)
Moderate reduction	5.5	16.2	10.7 (4.2, 17.3)	3.82 (1.58, 9.25)
Optimal reduction	3.3	13.4	10.0 (-0.6, 20.7)	7.73 (0.71, 84.27)
Long term OCS				
% With:	N=311*	N=1066*		
Increased dose	14.3	8.6	-5.7 (-18.0, 6.5)	0.51 (0.12, 2.17)
Low reduction	73.6	68.5	-5.1 (-22.5, 12.3)	0.94 (0.69, 1.28)
Moderate reduction	4.2	8.9	4.8 (-1.7, 11.2)	2.55 (0.78, 8.37)
Optimal reduction	7.9	14.0	6.1 (-7.7, 19.9)	4.16 (0.21, 82.18)

Results are expressed as marginal difference in absolute % probability [95% confidence interval] and relative risk [95% confidence interval]

Increased dose (<0% reduction), low dose reduction (0% to ≤50%), moderate dose reduction (>50% to ≤75%), and optimal dose reduction (>75%).

*Number of time-series observations; sample sizes vary as outcomes not reported for all patients. N numbers provide for each category for biologic not initiated and initiated groups, respectively. Total OCS: total (n=331/n=1071); increased dose (n=89/n=118); low reduction (n=203/n=464); moderate reduction (n=21/n=173); optimal reduction (n=18/n=316); LTOCS: total (n=311/n=1066); increased dose (n=48/n=86); low reduction (n=220/n=597); moderate reduction (n=12/n=123); optimal reduction (n=31/n=260).

Abbreviations: Bx: biologic; CI: confidence interval; OCS: oral corticosteroid

Table 3: Effectiveness of biologic initiation versus non-initiation on asthma control* and new incidence of OCS-related comorbidities† in 365 days.

	Bx not initiated	Bx initiated	Marginal difference in % probability (95% CI)	Relative risk (95% CI)
Asthma control				
% Patients:	N=177‡	N=354‡		
Well controlled	49.5	51.1	1.6 (-22.0, 25.2)	1.04 (0.58, 1.84)
Partly controlled	20.3	28.5	8.1 (-16.1, 32.3)	1.57 (0.46, 5.38)
Uncontrolled	30.2	20.5	-9.7 (-22.7, 3.2)	0.66 (0.37, 1.16)
Comorbidity incidence				
% patients with:	N=252‡	N=380‡		
Any OCS-related	0.18	2.31	2.13 (-1.81, 6.07)	12.74 (1.12, 144.82)
Any chronic OCS-related	0.11	2.00	1.88 (-1.58, 5.35)	26.02 (0.22, 3025.63)

Results are expressed as marginal difference in % probability (95% confidence interval) and relative risk (95% confidence interval)

* assessed by GINA control criteria, Asthma Control Test or Asthma Control Questionnaire;

†new OCS-related co-morbidities include: osteoporosis, heart failure, myocardial infarction, stroke, pulmonary embolism, glaucoma, cataract, renal failure, depression, anxiety, T2 diabetes, peptic ulcer, pneumonia, obstructive sleep apnea; OCS-related chronic co-morbidities include: osteoporosis, heart failure, myocardial infarction, stroke, pulmonary embolism, glaucoma, cataract, renal failure, T2 diabetes, peptic ulcer, obstructive sleep apnea;

‡Number of patients; sample sizes vary as outcomes not reported for all patients. N numbers provide for each category for biologic not initiated and initiated groups, respectively. Asthma control: total (n=177/n=354); well-controlled (n=83/n=164); partly controlled (n=50/n=104); uncontrolled (n=44/n=86); comorbidity incidence: total (n=9/n=70); any OCS-related (n=6/n=39); any chronic OCS-related (n=3/n=31)

Abbreviations: Bx: biologic; CI: confidence interval; OCS: oral corticosteroid

Table 4: Healthcare Resource Utilization in 365 days

Outcome	Bx not initiated	Bx initiated	Marginal Difference	Relative Risk (for Risk) / Rate Ratio (for Rate)
	N=502*	N=661*		
Risk of ED Visit	14% [9%, 20%]	6% [4%, 7%]	-9% [-14%, -3%]	0.35 [0.21, 0.58]
Rate of ED Visit	0.33 [0.12, 0.55]	0.12 [0.05, 0.20]	-0.21 [-0.37, 0.05]	0.26 [0.14, 0.48]
	N=514	N=667		
Risk of Hospitalization	12% [8%, 16%]	5% [4%, 7%]	-7% [-10%, -3%]	0.31 [0.18, 0.52]
Rate of Hospitalization	0.23 [0.13, 0.33]	0.10 [0.06, 0.14]	-0.13 [-0.23, -0.04]	0.25 [0.13, 0.48]

*N = per-patient observation used in the regression analysis
Abbreviations: ED: emergency department

Figure Legend

Figure 1: Subject disposition. HOCS: high oral corticosteroid exposure. * long-term use of OCS for at least 1 year or ≥4 courses of rescue steroid bursts during the 12-month baseline (pre-index) period. OCS: oral corticosteroid; HOCS: high oral corticosteroid exposure

Figure 2: **Comparison of pre- and post-propensity score matching baseline characteristics. SMD: standard mean difference between biologic-initiated and not-initiated groups**. AR: allergic rhinitis; BEC: blood eosinophil count; BMI: body mass index; CRS: chronic rhinosinusitis; NP: nasal polyps. The matched cohort included data on 996 patients who initiated biologics and 996 patients who did not. These patients were matched for baseline characteristics shown on the Y-axis. Patients were not matched by baseline characteristics in the unmatched cohort which comprised 996 patients who initiated biologics and 416 who did not initiate biologics.

Figure 3: **Change from baseline in (A) mean exacerbation rate/year*, (B) asthma control†, (C) asthma-related emergency department visit and (D) asthma-related hospitalization in those who initiated and did not initiate biologic therapy.** *defined as an event requiring rescue oral corticosteroids in the past year; †Asthma control was defined by either GINA Asthma Control Criteria,[1] Asthma Control Questionnaire,[29] or Asthma Control Test[30] in different settings. Bx: biologic

Figure 4: **Effectiveness of biologic initiation versus non-initiation on mean exacerbation rate (in the next 365 days)* reduction in patients with severe asthma and high oral corticosteroid exposure.** Results are expressed as marginal rate difference [95% confidence interval] and rate ratio [95% confidence interval]. BMI: body mass index; Bx: biologic; * sample sizes vary as outcomes not reported for all patients. N numbers of per-patient observation used in the regression provided for each category for biologic not initiated and initiated groups, respectively: overall (n=634/n=801); 18-34 (n=127/n=111); 35-54 (n=251/n=345); ≥55 (n=256/n=345); male (n=174/n=316); female (n=460/n=485); smoker (n=63/n=18); ex-smoker (n=128/n=219); non-smoker (n=443/n=219); underweight (n=87/n=11); normal weight (n=137/n=216); overweight (n=175/n=256); obese (n=236/n=318); Grade 0 (n=25/n=3); Grade 1 (n=28/n=24); Grade 2 (n=86/n=51); Grade 3 (n=496/n=719) and exacerbation defined as an event requiring rescue oral corticosteroids in the past year. Eosinophilic phenotype grades (0-3) are defined according to a previously published algorithm (**Figure E1**).[6]